REMARKS

Claims 1-3, 7-27 and 31-48 are pending. All of the claims have been rejected. Claims 1, 23 and 24 have been amended to more clearly recite that the virtual library is a non-enumerated virtual combinatorial library. This amendment, which does not alter the scope of the claims, is supported by the specification at p. 11, lines 21-22. In addition, claims 1, 23-25, 47 and 48 have been amended to more clearly state randomly selecting the set of N enumerated compounds. This is supported by the specification at for example, p. 18, ll. 9-28, p. 20, ll. 14-16 and p. 21, ll. 21:17-19. Claims 19 and 43 have been amended to correct a typographical error (to change "know" to "known" in claims 19 and 43 and change "compounds" to "compound" in claim 19) and to more clearly recite the similarity measures that can be used. Support for the amendment is found, *e.g.*, at p. 24, lines 13 to 14. In addition, one of ordinary skill in the art would recognize that pairwise similarities between a query structure and sets of enumerated compounds could include similarities in structure or similarities in surface characteristics.

Summary of Telephonic Examiner Interview on October 17, 2003

Applicant thanks the Examiner for granting a telephonic interview on October 17, 2003. Rejections based on Tokizane *et al.* and Young *et al.* were discussed. During the Examiner Interview on October 17, 2003, Applicant clarified to the Examiner that the term "building block" as used in the claims in the instant application defines reagents which have undergone virtual (or actual) chemical transformations, in contrast to individual component atoms in substructures of stored generic structures which have not been selected on the basis of their synthetic origin, and are not capable of undergoing chemical transformations to form enumerated compounds. Applicant indicated that it would identify portions of the specification which make clear that the building blocks are distinguishable from the atoms used to define stored generic structures in the Tokizane *et al.* reference. The Examiner agreed that support in the specification for Applicant's interpretation of "building block" would appear to distinguish Tokizane *et al.* The specification of the instant application at page 11, lines 25-27 makes clear that the enumerating step of the claimed invention starts with reagents, and that chemical transformations are performed on those reagents to generate the N enumerated compounds. Following selecting of the M compounds, the selected M compounds are then deconvoluted into their reagents, and a focused library can be generated from those reagents. Specification at page 4, lines 4-7. For the

reasons set forth in more detail below, Applicant therefore respectfully asserts that the current claims are distinguishable from Tokizane *et al.*

With respect to Young *et al.*, Applicant noted, and the Examiner agreed that Young *et al.* disclosed identifying a molecular fragment by obtaining a computerized representation of the three-dimensional structure of a binding site on the surface of a biological macromolecule, and then generating a library of compounds, each of which contained the molecular fragment. Applicant proposed amending the claim to more clearly state the step of "randomly selecting a set of N reagent combinations" such that not all of the N compounds obtained from enumerating the N reagent compounds would contain the same reagent. The Examiner agreed that the proposed amendment appeared to distinguish Young.

Rejection under 35 § 102(e)(2) --Tokizane et al.

The Examiner has rejected claims 25-27, 31-37, 47 and 48 under 35 U.S.C. § 102(e)(2) as being clearly anticipated by Tokizane *et al.* (U.S. Patent No. 4,811,217). Applicants respectfully traverse this rejection. The Examiner refers to the previous Office Action, mailed 9/26/02 for "the focused library teaching" which the Examiner states is "disclosed as a search utilizing a query structure such as structure 2 to result matches which are clearly focused thereby."

As correctly noted by the Examiner, the method of Tokizane *et al.* describes substructure searching. That is, it provides a method to identify the subset of chemical structures in a database of chemical structures that contain a specific query substructure of interest. Stored structures, such as the one set forth in Figure 1, are broken down into query nodes consisting of non-hydrogen component atoms or groups. Tokizane *et al.* at col. 5, ll. 1-3 ("First, all of the atoms (including generic atoms) except for hydrogen atoms, which will be called nodes hereafter, are numbered at will."). The query nodes are individually assigned values based on specific connectivity patterns, i.e., atoms and bonds. Thus, the values assigned to the various query nodes are not based on their synthetic origin, *i.e.*, the stored structures in Tokizane *et al.* are not "deconvoluted into component reagent parts" (building blocks). The result of a substructure search by the query node system described in Tokizane *et al.* is therefore a list of compounds that share a common substructure but were not selected because they share common synthetic routes. As such, Tokizane *et al.* fails to teach "deconvoluting said M compounds into

associated building blocks" and "extracting an enumerated focused library based on said building blocks" as recited in claims 25-27, 31-37, 47 and 48.

Enumeration is described by the present invention as "the process of constructing computer representations of a structure of one or more products associated with a virtual combinatorial library. Enumeration is accomplished by starting with reagents and performing chemical transformations, such as making bonds and removing one or more atoms, to construct explicit product structures." Specification at p. 11, lines 25-27 (emphasis added). Page 4, lines 4-7 of the specification, further indicates that after "M number of compounds of the first set of enumerated compounds are selected based on a fitness function," "[t]he M compounds are then deconvoluted into reagents to generate a focused library."

By failing to teach the steps of deconvoluting M compounds into associated building blocks and then extracting an enumerated focused library based on said building blocks. Tokizane *et al.* does not teach or suggest, alone or in combination with any of the other cited references, the generation of a focused library from reagents (building blocks), as recited in independent claims 25, 47, and 48. Moreover, claims 26,27, and 31-37 depend from claim 25 and are therefore patentable for at least the reasons discussed above with respect to independent claim 25. Applicant therefore respectfully requests reconsideration and withdrawal of the instant rejection.

Rejection under 35 § 102(b) –Young et al.

The Examiner has also maintained the rejection of claims 1-3, 7-27, and 31-48 under 35 U.S.C. 102(b) as being anticipated by Young *et al.* (EP 0,818,744). Applicants also respectfully traverse this rejection.

Young *et al.* relates to the generation of sets of lists of virtual libraries consisting of a molecular fragment containing a plurality of substituents. The molecular fragment is identified by obtaining a computerized representation of the three-dimensional structure of a binding site on the surface of a biological macromolecule, generating a computerized model of the functional structure of said binding site which can be used to identify interactions between the binding site

and a drug candidate molecule, and identifying a molecular fragment capable of placement within the binding side and capable of carrying one or more substituent groups. *See* Young *et al.* at p. 3-4 (reciting steps (1)-(4) in the described method). Thus, in Young *et al.*, all of the members of the virtual library contain the same molecular fragment with various attached substituents wherein the molecular fragment has been selected based on favorable interactions between the computerized representation of the three-dimensional structure of a binding site. *See* Young *et al.* at front page, paragraph (57); *see also,* Young *et al.* at page 8, ll. 3-5 ("In the process of the invention, each member of the virtual library consists of a common template with different substituents attached to it.").

In contrast, the presently claimed method in claim 1 contains the elements of randomly selecting a set of N reagent combinations from a virtual library, enumerating said set of N compounds, selecting M compounds from the set of N enumerated compounds, deconvoluting the M compounds into their associated building blocks, and generating a focused library. As a specific distinction from Young *et al.*, the presently claimed method in claim 1 contains the elements of randomly selecting a set of N reagent combinations from a virtual library. For example, the reagent combinations can be randomly selected by randomly selecting reagents (building blocks) from one or more classes of reagents that can undergo chemical transformation to form the reagent combinations. *See, e.g.,* Specification at p. 18, ll. 9-28; p. 20, ll. 14-16; and p. 21, ll.17-19.

In addition, the focused libraries of this invention do not consist of a single template containing various attached substituents; and embodiments of the presently claimed invention are effective to reduce computational requirements because they do not require generating, listing or storing all of the compounds in the starting virtual library.

In contrast, Young *et al.* teaches generating a list of all of the compounds in a virtual library, where each of the compounds contains the same molecular fragment, or template, to which different substituents can be attached. For instance, on page 6, lines 3-5, Young *et al.* defines a "virtual library" as "the set of compounds theoretically attainable by the inter-reaction of the reagents in the reagent lists for that library" and Young *et al.* further notes that in "the process of the invention, each member of the virtual library consists of a common template with

different substituents attached to it." Moreover, Young *et al.* does not suggest the selection of only selected members of a combinatorial virtual library as a method to reduce computational requirements. In fact, Young *et al.* teaches away from this by suggesting limiting the precision of the computer evaluation in order to reduce computational requirements:

> Computational requirements may also readily be reduced by limiting the precision of the computer evaluation and ranking of the virtual libraries for the initial performance of steps (5) and/or (6), *e.g.*, by limiting the conformational freedom of the compound under evaluation or by specifying the position and orientation of the compound within the binding site model.

Young *et al.* at page 6, lines 23-26.

Thus, Young *et al.* does not teach or suggest, among other elements, randomly selecting a set of N reagent combinations from a virtual library, enumerating the set of N compounds, selecting M compounds from the set of N enumerated compounds, deconvoluting the M compounds into their associated building blocks, and generating a focused library as required by the claims of the pending application.

CONCLUSION

In view of the foregoing, Applicant asserts that the rejection of Claims 25-27, 31-37, 47, and 48 under 35 U.S.C. § 102(e)(2) and the rejection of Claims 1-3, 7-27, and 31-48 under 35 U.S.C. § 102(b) are traversed and should be withdrawn. As shown above, the claims are allowable. Accordingly, favorable action is requested.

The amendments made herein introduce no new matter and their entry is respectfully requested. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Applicant encloses a one-month Petition for Extension Time. Please charge the fee, and any additional fee that may be required in connection with the enclosed response, to Deposit Account No. 50-2212, Order Number 044988.030.4557.

Respectfully submitted,

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